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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/646,924	09/25/00	RASPE	E	MERCK 2157

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EXAMINER	
CHUNDURU, S	
ART UNIT	**PAPER NUMBER**
1656	10

DATE MAILED: 11/01/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/646,924	Applicant(s) RASPE ET AL.	
	Examiner Suryaprabha Chunduru	Art Unit 1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicants' response to the office action (Paper No. 8) filed on August 17, 2001 has been entered.

2. New claims 19-22 were added. The claims 1-22 are pending in this Application and are considered for examination in this office action.

New Grounds of Rejection Necessitated by Amendment

3a. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for ROR, does not reasonably provide enablement for functional equivalents of the ROR receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the instant claims.

The instant claims are broadly drawn to a method for screening a substance for usefulness in the treatment of a lipid metabolism dysfunction comprising contacting said substance with a ROR receptor, a response element, or a functional equivalent thereof. The specification solely teaches the ROR receptor and provides absolutely no teaching or suggestion regarding functional equivalents of the receptor or any specific chimeric protein having ligand binding sites comparable to that of ROR that would teach an ordinary practitioner which chimeric protein having ligand binding sites which would function theoretically/ practically targeting the instant method. There are no actual working examples of analysis of functional equivalents of the ROR

receptor in the specification. There is no actual working examples of the broadly claimed ~~tub~~ gene in the specification. The prior art supports the unpredictability of the broad claims. Wiesenberg et al. (USPN. 5,958,683) states that 'nobody could expect or predict that these compounds function as ligands of the RZR/ROR receptor family, too' (see column 2, lines 26-27). Thus unpredictability is buttressed by the prior art where the binding of a compound to ROR receptor was used expressly and deemed unpredictable. It would require extensive experimentation involving all functional equivalents of ROR, receptor and testing to determine whether all functional equivalents functioned as required by the claims. Therefore, in view of the breadth of the claims, the absence of guidance provided by the specification, the absence of teaching in the prior art, the absence of any working examples, the unpredictability of the art and the large quantity of experimentation necessary, it is concluded that undue experimentation is required to make and use the invention as broadly claimed.

3b. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The current claims are drawn to a method for identifying a compound useful for the treatment of lipid metabolism dysfunction which comprises a ROR receptor and its functional equivalents thereof. This large genus of functional equivalents of ROR receptor is represented in the specification by the broad term 'functional equivalents'. Thus, applicant has express possession of only one species, the ROR receptor itself, in a genus, which comprises hundreds of millions of different possibilities (such as ROR receptor equivalent having binding sites for

compounds with antiarthritic and auto-immune activity). The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common elements or attributes of the ROR receptor functional equivalents are disclosed in the specification, which could give a clear definition of the functional equivalents. Further no information is given regarding a methodology to determine such common elements or attributes.

> It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, the broadly claimed tub gene is not defined clearly. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

3c. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

i) Claims 1, 3-4, 8, 16, and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims are indefinite and unclear for reciting 'functional equivalent thereof'. It is unclear what the term accomplishes for.

ii) Claims 3, 7, and 22 recites the limitation "the RNA polymerase / the yeast nuclear factor Gal4 , the DNA binding domain and the DEF domains " in screening a substance. There is insufficient antecedent basis for this limitation in the claim. The specification does not teach all the limitations of the instant claims and lacks experimental basis for these limitations. Therefore, the instant claims are rejected for lack of antecedent basis.

iii) Claims 3, 16, and 22 are indefinite over the recitation of "capable of functionally coupling" because capability is a latent characteristic and the claims do not set forth the criteria by which to determine capability. That is, it is not clear whether the recited probes have the potential to functionally couple or do in fact do functionally couple to the recited target. Amendment of the claim to read, for example, "which functionally couple" would obviate this rejection.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiesenberg et al. (USPN. 5,958,683) and in view of Fraser et al. (J Biol Chem., vol. 272(21): 13892-13898, 1997).

Wiesenberg et al. teach a method for screening compounds that bind to RZR/ROR receptor family, wherein Wiesenberg et al. disclose that the method comprises contacting a compound (substance) to be tested with a RZR/ROR receptor being combined with response element and measuring the level of signal (see column 19, lines 24-33, claim 1).Wiesenberg et al. further disclose that (i) the method also comprises cotransfection of a host with a construct having ROR receptor with one or more response elements and a reporter gene and measuring the expression of reporter gene in the presence of test compound (see column 19, lines 44-54, claim 60; (ii) reporter gene was selected from chlororamphenicol acetyltransferase (CAT), beta-galctosidase (lacZ) or luciferase (see column 20, lines 28-31, claim 15); (iii) the host cell was selected from a bacterial, fungal, insect , mammalian cell, yeast or drosophila (see column 19, lines 61-65, claims 10-11); the method of screening could be determined using transfection and analysis of gene expression in vitro (see column 12, lines 39-67, column 13, lines 1-14, column 5, lines 1-17); the method was used to use the novel ligands identified by the method to treat autoimmune diseases (see column 5, lines 18-26). However, Wiesenberg et al. did not teach the expression of apo C-III.

Fraser et al. teach a method for modulating apo C-III gene expression in the presence of a hepatocyte nuclear factor 4 (HNF-4), a member of ROR family, wherein Fraser discloses that

HNF-4 binds to apolipoprotein promoter sequences (based on recombinant promoter-reporter constructs) and induction of apo C-III expression by HNF-4 (see page 13897, paragraph 1 and page 13898, paragraph, 2). Fraser et al. also disclose that the high levels of apo C-III correlate with increased fasting triglycerides in both clinical hypertriglyceridemic patients and murine model systems and the high serum triglycerides are directly atherogenic (see page 13898, paragraph 2). Further, Fraser et al. disclose the modulation of apo C-III expression via HNF-4 might represent a potential therapeutic target (see page 13898, paragraph 2).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of screening compounds that bind to RZR/ROR receptor family as taught by Wiesenberg et al. with the method of modulation of apo C-III expression via HNF-4 as taught by Fraser et al. which is applicable to the treatment of atherosclerosis because Wiesenberg et al. states that 'ligands of the RZR/ROR receptor family hve anti-autoimmune, anti-arthritic and or anti-tumor activity. Which implies that the binding of the ligand to the receptor enhances the affinity of the receptor to specific DNA regions (so called hormone response elements) in genes, which are involved in the regulation of cell proliferation and /or differentiation. The transcription of these response genes is either up or downregulated after binding of the ligand-receptor complex. Based on this novel observation it is now possible to use this receptor family for the screening of further compounds (ligands)' (see column 2, lines 26-40). One such transcriptional response expressly motivated by Fraser et al. is the use of ROR family member, HNF-4 in the regulation of apo C-III expression to examine the effects of modulating HNF-4 transcriptional activity on the endogenous expression levels of the apo AI and apo C-III genes' (see page 13892, column 2, paragraph 1). An ordinary practitioner would

have been motivated to combine the method of Wiesenberg et al. with the method of Fraser et al. in order to achieve the expected advantage of a rapid and sensitive method for screening compounds that bind to RZR/ROR.

Response to Arguments

5. Applicants response to the office action (Paper No.8) is fully considered and deemed persuasive in part.

6. The objection made in the previous office action for drawings is withdrawn herein in view of applicants, amendment (Paper No.8).

7. The rejection made in the previous office action under 35 USC 101 is withdrawn herein in view of applicant's amendment (Paper No. 8).

7. The rejection made under U.S.C. 112 second paragraph is withdrawn herein in view of the applicants' amendment (Paper No.8).

8. Applicant's arguments with respect to the rejection made under U.S.C. 103(a) to claims 1-18 have been considered but are moot in view of the applicants' amendment and arguments (Paper No. 8) and in view of the new ground(s) of rejection.

No claims are allowable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 703-305-1004. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 703-308-1152. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-308-0294 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
October 26, 2001

JEFFREY FREDMAN
PRIMARY EXAMINER